INFLUENCE OF GLYCEROL ON THE POLYMORPHIC BEHAVIOR OF SOLID TRIGLYCERIDE NANOPARTICLES STABILIZED WITH POLY(VINYL ALCOHOL)

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ABSTRACT

Colloidal dispersions of lipids, e.g. triglycerides, are under intensive investigation as drug delivery systems. Solid triglyceride nanoparticles exist in different polymorphic modifications. The aim of this study was to investigate the effects of the addition of glycerol, which can be used for the isotonization of such dispersions, on the polymorphic behavior of poly(vinyl alcohol)-stabilized tripalmitin nanoparticles. Glycerol was added to the nanoparticle dispersions at different concentrations in the heat.

The dispersions were investigated for their thermal behavior and storage stability with regard to particle size and polymorphic transitions of the triglyceride matrix, using photon correlation spectroscopy, differential scanning calorimetry and X-ray diffraction. The addition of glycerol led to a decreasing crystallization temperature of the nanoparticles and slowed down the polymorphic transition into the stable β-modification.

Keywords: Triglyceride nanodispersions, crystallization, polymorphism.

INTRODUCTION

Lipid nanoparticles are under intensive investigation as drug delivery systems for poorly-water soluble drugs [Bunjes, 2010]. Many of the lipids used for the preparation, for example triglycerides, are polymorphic substances. Triglycerides occur in three different crystal modifications: the metastable α- and β'-modification and the stable β-modification. These modifications differ from each other in their physicochemical properties, which might have an influence on the drug loading capacity [Westesen, 1997].

After crystallization, triglyceride nanoparticles undergo polymorphic transitions from the metastable α- into the stable β-modification, sometimes via the β'-modification. These transitions are monotropic and depend on several factors, like matrix composition as well as the type of emulsifier used, additives or storage conditions.

The aim of this study was to investigate the influence of the additive glycerol, which is often used for isotonization of triglyceride nanodispersions, on the polymorphic behavior of the lipid nanoparticles.

RESEARCH CONCEPT

A dispersion consisting of 10 % tripalmitin (Dynasan 116®, Condea), 10 % PVA (Mowiol® 3-83, Clariant), and bidestilled water in which PVA was dissolved (all concentrations w/w) was prepared by melt homogenization. First, the lipid and the aqueous phase were heated at ~80 °C separately. Both phases were combined and prehomogenized with an ultra-turrax (IKA T25 digital Ultra-Turrax; S25N-10G, Ika-Werke) at 13.000 rpm for 4 min. The predispersion was homogenized in a Microfluidizer M110S instrument (Microfluidics) for 10 cycles at 800 bar and ~80 °C. The hot dispersion was divided into 10 ml fractions which were allowed to cool to 40 °C. In order to set the glycerol content, the fractions were combined with 10 ml of a glycerol-containing solution and incubated at

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40 °C for 30 min. The dispersions were cooled to 5 °C for 30 min to crystallize the nanoparticles and subsequently stored at 20 °C. The final dispersions contained 5 % triglyceride, 5 % PVA and 0 %, 1 %, 2 %, 5 %, 10 %, 15 % and 20 % glycerol, respectively.
Particle size was measured by photon correlation spectroscopy (PCS) with a Zetasizer Nano ZS instrument (Malvern) at 25 °C and an angle of 173 °. The dispersions were diluted with purified and particle-free water. The z-average diameter and PDI were given as mean of three measurements of 5 min each after 5 min of equilibration.

Differential scanning calorimetry (DSC) measurements were performed in a DSC 1 Star^e System with a full range sensor (FRS 5) and a sample robot (Mettler Toledo GmbH). About 15 µl of the dispersions were accurately weighed into aluminum crucibles that were cold sealed. The samples were heated to 85 °C with a heating rate of 10 °C/min, held at that temperature for 5 min, cooled to -5 °C (10 °C/min) and heated again to 85 °C (10 °C/min). All measurements were performed against an empty reference crucible and under nitrogen purge. The enthalpies observed were normalized for the weight of the samples.
The melting enthalpies were used to approximate the fraction of particles in the different polymorphic forms. To determine the fraction of particles in the stable β-modification, the enthalpy values of the β-form melting transition were calculated according to [Joseph, 2015]. A small amount of the dispersions was tempered at 37 °C for 96 h to obtain a β-reference dispersion. The complete transition of this sample into the β-polymorph was confirmed with X-ray diffraction.

X-ray measurements were performed with a small- and wide-angle X-ray diffraction setup (SAXSess, Anton Paar), equipped with a copper anode (λ = 1.54 nm). The sample was measured in a quartz capillary sample holder in 25 runs of 30 s each at 20 °C.

RESULTS

All dispersions had a milky white appearance with a z-average diameter of about 80 nm and a narrow particle size distribution with PDI values between 0.10 and 0.12. DSC investigations revealed that all nanoparticles were in the metastable α-polymorph directly after preparation. Almost no differences were observed for the different samples during the first heating step. X-ray diffraction patterns confirmed that all particles were present in the metastable α-polymorph with only marginal differences in the diffractograms for samples with different glycerol content. During cooling in the DSC, the samples displayed a linearly decreasing crystallization temperature with increasing glycerol content (Fig. 1).

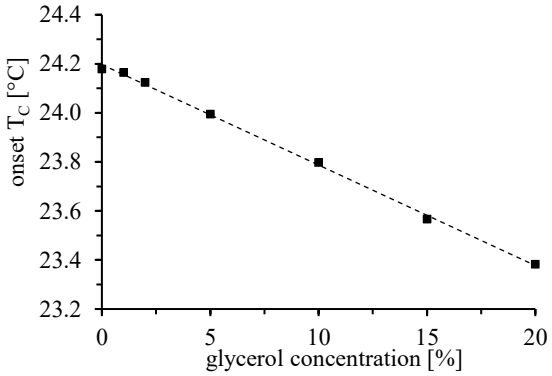

Fig. 1: Onset of crystallization events for dispersions with increasing glycerol concentration.

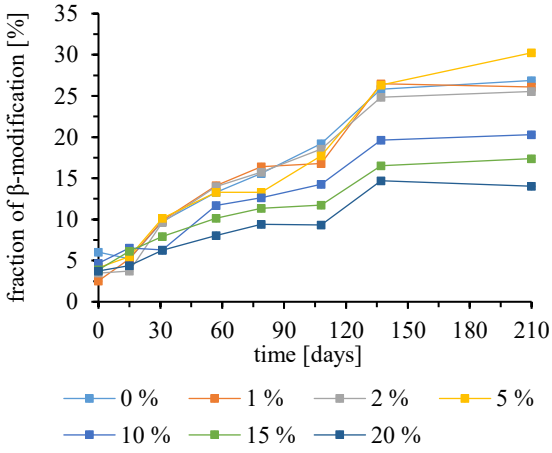

Fig. 2: Fraction of nanoparticles in the β-modification after storage at 20 °C as determined by DSC.

Over a storage time of about 7 months at 20 °C, the transition of nanoparticles into the stable β-modification distinctly slowed down with increasing glycerol content (Fig. 2). After storage, the fraction of particles in the stable β-modification varied from 25 % (0 % glycerol) to 15 % (20 % glycerol).

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DISCUSSION

The use of PVA as emulsifier in solid triglyceride nanoparticles led to the formation of the α-modification with a remarkable stability in agreement with previous studies with tristearin nanodispersions [Rosenblatt, 2008; Joseph, 2015]. The addition of glycerol after homogenization did not change the particle size of the dispersions noticeably but influenced the crystallization temperature as well as the polymorphic behavior of the lipid nanoparticles.

The decrease in crystallization temperature may indicate a change of the composition of the nanoparticles as it is, for example, obsorved upon drug loading of triglyceride nanoparticles [Roese, 2017]. As the polarity of glycerol is very high it is unlikely that it interacts with the matrix lipid itself. Instead, it may modify the interaction between PVA and the lipid. The assumed increase in interaction could be an explanation for the higher stability of the metastable α-polymorph in samples containing a high concentration of glycerol.

CONCLUSIONS

In dispersions of PVA-stabilized tripalmitin nanoparticles, the addition of glycerol leads to a decrease in crystallization temperature and slows down the polymorphic transition into the stable β-modification. It is unlikely that glycerol molecules are distributed into the particles due to their high polarity. A possible cause for the observed phenomena could be a specific interaction between glycerol and PVA which affects the composition of the nanoparticles. However, the exact mechanism is still unclear and remains to be elucidated.

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